90-001159

Europäisches Patentamt
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Publication number 0 347 773 A1

EUROPEAN PATENT APPLICATION

Application number: 89110986.0

Date of filing: 16.06.89

Int Cl.⁴ C07D 231/54 , A61K 31/425 , C07D 401/04 , C07D 491/048 , C07D 495/04

Priority: 20.06.88 GB 8814587

Date of publication of application 27.12.89 Bulletin 89/52

Designated Contracting States: ES GR

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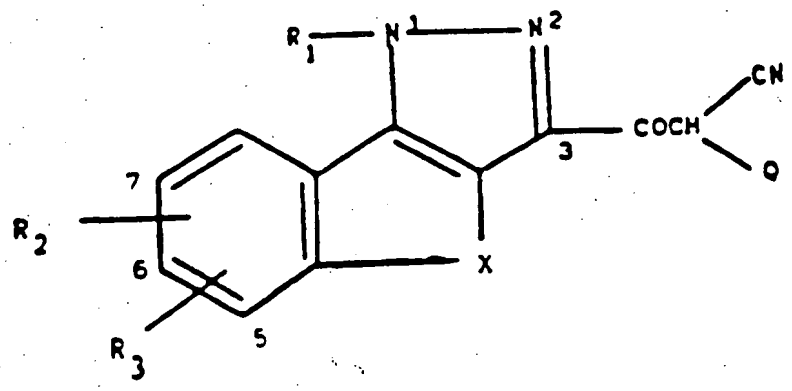
Condensed Pyrazole 3-oxo-propanenitrile derivatives and process for their preparation.

Condensed pyrazole 3-oxo-propanenitrile derivatives of formula (I)



(I)

wherein X represents a -CH(R_a)- group, an oxygen atom or a -S(O)$_n$- group where n is 0, 1 or 2; R_1 represents C$_1$-C$_4$ alkyl, pyridyl or unsubstituted or substituted phenyl; R_2, R_3 and R_a are as defined herein, and Q represents hydrogen, carboxy, C$_2$-C$_7$ alkoxycarbonyl or a -CON(R_a)R_b group, R_a and R_b being as defined herein; and their pharmaceutically acceptable salts have immunomodulating activity and can be used in particular as immunostimulating agents, e.g. in the treatment of acute and chronic infections of both bacterial and viral origin, alone or in association with antibiotic agents, and in the treatment of neoplastic

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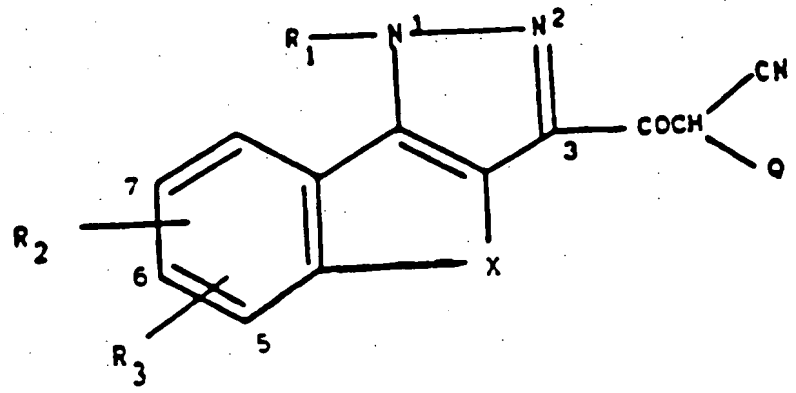
diseases, alone or in association with antitumoral agents, in mammals.

CONDENSED PYRAZOLE 3-OXO-PROPANENITRILE DERIVATIVES AND PROCESS FOR THEIR PREPARATION

The present invention relates to condensed pyrazole 3-oxo-propanenitrile derivatives, to a process for their preparation and to pharmaceutical compositions containing them.

The compounds of the invention have the general formula (I)



(I)

wherein

X represents:

a) a

group wherein R_4 is hydrogen, C_1-C_6 alkyl or a

group wherein each of R' and R'' independently is C_1-C_6 alkyl or R' and R'', taken together with the nitrogen atom to which they are linked, form a heterocyclic ring which is selected from N-pyrrolidinyl, N-piperazinyl, hexahydroazepin-1-yl, thiomorpholino, morpholino and piperidino and which is unsubstituted or substituted by C_1-C_6 alkyl; or

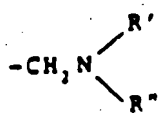
b) an oxygen atom or a $-S(O)_n-$ group, wherein n is zero, 1 or 2, R_5 represents C_1-C_6 alkyl, pyridyl or phenyl, the phenyl being unsubstituted or substituted by one or two substituents chosen independently from halogen, trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, nitro, amino, formylamino and C_2-C_8 alkanoylamino; each of R_2 and R_3 is independently

a') hydrogen, halogen, C_1-C_6 alkyl or trifluoromethyl,

b') hydroxy, C_1-C_6 alkoxy or C_3 or C_4 alkenyloxy,

c') nitro, amino, formylamino or C_2-C_8 alkanoylamino,

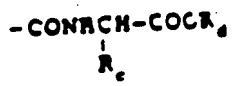
d') di(C_1-C_6 alkyl)amino or a



wherein R' and R'' are as defined above

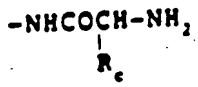
e) CH_2OH, CHO, COOH or C_2-C_7 alkoxycarbonyl,

f) a



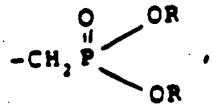
group wherein R_a is hydrogen or C_1-C_4 alkyl and R_c is hydrogen, phenyl or the side-chain of an α-aminoacid;

g) a



group, wherein R_c is as defined above

h) a

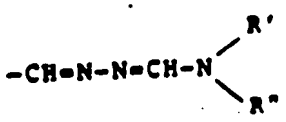


a $-CH_2OCO(CH_2)_nCOOR$ or a $-NHCO(CH_2)_nCOOR$ group, wherein n is as defined above and R is hydrogen or C_1-C_6 alkyl;

k) a $-CH=N-OR'$ group wherein R' is hydrogen or a $-CH_2COOH$ group;

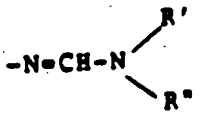
i) a $-CH=N-NH-R'_2$ group wherein R'_2 is hydrogen, $-CH_2CH_2OH$, C_2 or C_3 alkoxycarbonyl or a $-(CH_2)_p-R'_3$ group wherein p is 1 or 2 and R'_3 is COOH or C_2-C_7 alkoxycarbonyl;

l) a



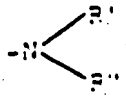
group wherein R' and R'' are as defined above, or

m) a

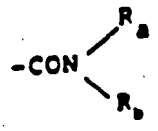


group wherein R' and R'' are as defined above; or

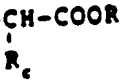
n) a C_2-C_7 alkoxycarbonyl group substituted by a



group, wherein R' and R'' are as defined above; and Q represents hydrogen, carboxy, C_1-C_4 alkoxycarbonyl or a



group wherein R_a represents hydrogen or C_1-C_{20} alkyl and R_b represents C_1-C_{20} alkyl, a

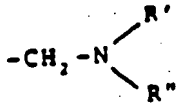


group wherein R and R_c are as defined above or a $-(A)_m-R_5$ group wherein m is zero or 1, A is a C_1-C_6 alkylene chain and R_5 is

a˝) C_5-C_8 cycloalkyl;

b˝) pyridyl, unsubstituted or substituted by one or two substituents chosen independently from halogen, C_1-C_6 alkyl and C_1-C_6 alkoxy;

c˝) phenyl, unsubstituted or substituted by one or two substituents independently chosen from halogen, CF_3, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, nitro, formylamino, C_2-C_6 alkanoylamino, di(C_1-C_6 alkyl)-amino, hydroxy, CH_2OH, COOH, C_2-C_7 alkoxycarbonyl, formyloxy, C_2-C_6 alkanoyloxy and a



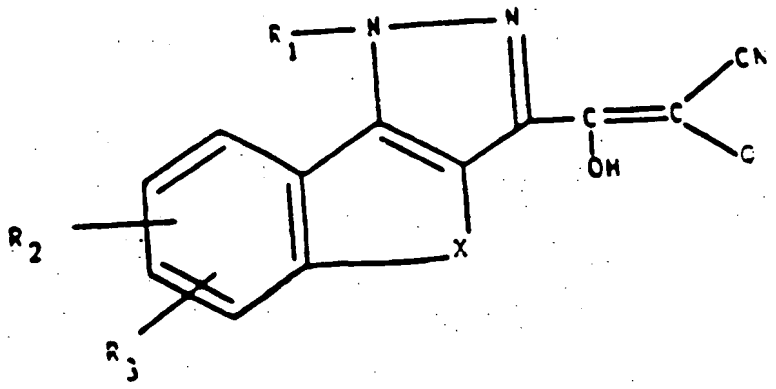
group wherein R˙ and R˝ are as defined above;

d˝) 2-thienyl, 2-furyl or 1-(C_1-C_6 alkyl)-pyrrol-2-yl; or

e˝) a heterocyclic ring which is selected from 2-pyrimidyl, 2-thiazolyl and 3-isoxazolyl and which is unsubstituted or substituted by C_1-C_6 alkyl;

and the pharmaceutically acceptable salts thereof.

The present invention includes within its scope all possible isomers, stereoisomers and optical isomers and their mixtures, and the metabolites and the metabolic precursors or bioprecursors of the compounds of formula (I). It has be to be noticed that the compounds of formula (I) may be represented also by a tautomeric structure, namely the enol structure of formula (Ia)



(Ia)

wherein

X, R_1, R_2, R_3 and Q are as defined above. However, the compounds of formula (Ia), which fall within the scope of the present invention too, are described in the present specification as compounds of formula (I).

A halogen atom is preferably chlorine or fluorine. The alkyl, alkylene, alkanoyloxy, alkoxy and alkanoylamino groups may be branched or straight chain groups.

A C_1-C_{20} alkyl group is preferably a C_1-C_6 alkyl group.

A C_1-C_6 alkyl group is, e.g., methyl, ethyl, propyl, isopropyl, butyl or tert.butyl, more preferably methyl

ethyl or tert butyl

A C_3 or C_4 alkenyloxy group is preferably allyloxy

A C_1-C_4 alkoxy group is, e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy or tert butoxy, preferably it is methoxy, ethoxy or propoxy

A C_5-C_8 cycloalkyl group is preferably cyclopentyl or cyclohexyl

A C_2-C_8 alkanoylamino group is preferably acetylamino or propionylamino

A C_2-C_8 alkanoyloxy group is preferably acetoxy or propionyloxy.

A C_2-C_7 alkoxycarbonyl group is preferably a C_2-C_5 alkoxycarbonyl group, in particular a C_2 or C_3 alkoxycarbonyl one. A C_1-C_4 alkylene chain is preferably a C_1-C_3 alkylene chain, such as a $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$.

$$-\underset{\displaystyle CH_3}{\overset{|}{CH}}- \quad \text{or} \quad -\underset{\displaystyle C_2H_5}{\overset{|}{CH}}-$$

chain.

A di(C_1-C_4 alkyl)amino is preferably a di (C_1-C_4 alkyl)amino group, in particular a di(C_1 or C_2 alkyl)-amino one. In a

$$-\underset{\displaystyle R_c}{\overset{|}{CH}}-COOR$$

group, wherein R is as defined above and R_c is as defined above except hydrogen, the asymmetric carbon atom to which $-R_c$ and -COOR are linked may have either the R or S configuration. The side-chain of an α-aminoacid is specifically the residue obtained from an α-aminoacid by removing the amino and the carboxy groups together with the α-carbon atom to which they are linked. The side-chain of an α-aminoacid as defined above is preferably the side-chain deriving from a naturally occurring aminoacid

Examples of such aminoacids are alanine, valine, leucine, isoleucine, phenylalanine, proline, hydroxyproline, serine, threonine, cysteine cystine, methionine, tryptophan, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine and phenylserine.

Preferred examples of said chains of the above mentioned aminoacids are $-CH_3$ (deriving from alanine), $-CH_2CH(CH_3)_2$ (deriving from leucine) and $-CH_2-C_6H_5$ (deriving from phenylalanine).

Examples of pharmaceutically acceptable salts are either those with inorganic bases such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases such as lysine, arginine, N-methylglutamine, triethylamine, triethanolamine, dibenzylamine, methylbenzylamine, di-(2-ethyl-hexyl)-amine, piperidine, N-ethylpiperidine, N,N-diethylaminoethylamine, N-ethylmorpholine, β-phenethylamine, N-benzyl-β-phenethylamine, N-benzyl-N,N-dimethylamine and the other acceptable organic amines, as well as the salts with inorganic acids, e.g. hydrochloric, nitric, hydrobromic and sulphuric acids and with organic acids, e.g. citric, tartaric, maleic, malic, fumaric, methanesulphonic and ethanesulphonic acids. Preferred salts of the compounds of formula (I) are the sodium and the potassium salts thereof.

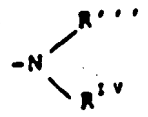
As stated above, the present invention also includes within its scope pharmaceutically acceptable bioprecursors (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above, but which nevertheless upon administration to a human being are converted directly or indirectly *in vivo* into a compound of formula (I).

Preferred compounds of the invention are the compounds of formula (I), wherein X is:

a'') a

$$-\underset{\displaystyle R'_4}{\overset{|}{CH}}-$$

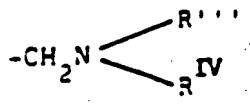
group wherein R'_4 is hydrogen, C_1-C_4 alkyl or a



group wherein each of R^{III} and R^{IV} independently is C_1 or C_2 alkyl or R^{III} and R^{IV}, taken together with the nitrogen atom to which they are linked, form a heterocyclic ring which is selected from N-pyrrolidinyl, N-piperazinyl, morpholino and piperidino and which is unsubstituted or substituted by methyl; or b") oxygen or a $-S(O)_n-$ group, wherein n is as defined above; R_1 represents unsubstituted pyridyl; or phenyl unsubstituted or substituted by one or two substituents chosen independently from halogen, trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, nitro, amino and C_2-C_8 alkanoylamino;

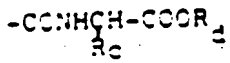
R_2 and R_3 each independently is

a°) hydrogen, halogen, hydroxy, COOH, CHO, CH_2OH, CF_3, C_2-C_7 alkoxycarbonyl, nitro, amino, C_1-C_4 alkyl, C_1-C_4 alkoxy or a



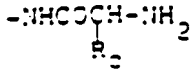
group wherein R^{III} and R^{IV} are as defined above;

b°) a



group wherein R^d is hydrogen or C_1-C_6 alkyl and R_c is hydrogen, phenyl or the side-chain of an α-amino-acid as defined above;

c°) a

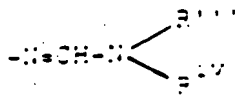


group, wherein R_c is as defined above;

d°) a $-CH_2OCO(CH_2)_nCOOR_d$ or a $-NHCO(CH_2)_nCOOR_d$ group, wherein n and R_d are as defined above;

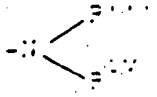
e°) a $-CH=N-OR_1$ group, wherein R_1 is hydrogen or a $-CH_2COOH$ group;

f°) a

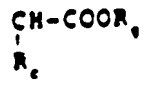


group wherein R^{III} and R^{IV} are as defined above;

g°) a C_2-C_6 alkoxycarbonyl group substituted by a

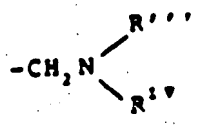


group, wherein R^{III} and R^{IV} are as defined above; Q represents hydrogen, C_2-C_5 alkoxycarbonyl or a $-CONR_aR_b$ group wherein R_a is hydrogen or C_1-C_6 alkyl and R_b is C_1-C_6 alkyl; a



group wherein R_9 is hydrogen or C_1-C_4 alkyl and R_c is as defined above, or a -(A)$_m$-R_5 group wherein m is zero or 1, A is a C_1-C_3 alkylene chain and R_5 is:

a^{IV}) unsubstituted pyridyl or phenyl unsubstituted or substituted by one or two substituents chosen independently from halogen, CF_3, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CH_2OH, COOH, di-(C_1-C_4 alkyl)amino, hydroxy, formyloxy, C_2-C_6 alkanoyloxy and a



group wherein R^{III} and R^{IV} are as defined above.

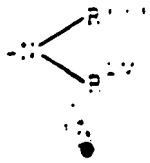
b^{IV}) 2-thienyl or 2-furyl, or

c^{IV}) a heterocyclic ring which is selected from 2-thiazolyl or 3-isoxazolyl and which is unsubstituted or substituted by methyl; and the pharmaceutically acceptable salts thereof

More preferred compounds of the invention are the compounds of formul (I) wherein X is oxygen, sulphur or a

group

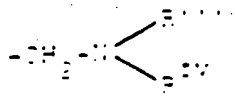
wherein R_4 is hydrogen, methyl or a



group

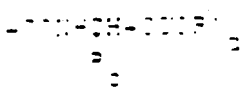
wherein R^{III} and R^{IV} are as defined above.

R_5 represents phenyl unsubstituted or substituted by a substituent selected from nitro, halogen, CF_3, C_1-C_4 alkyl and C_1-C_4 alkoxy; each of R_2 and R_3 independently is a**) hydrogen, halogen, COOH, CHO, CH_2OH, C_2-C_5 alkoxycarbonyl, CF_3, nitro, amino, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, or a



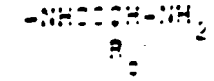
group wherein R^{III} and R^{IV} are as defined above.

b**) a



group, wherein R_4 is hydrogen or C_1-C_4 alkyl and R_5 is as defined above

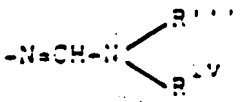
c**) a



group wherein R_c is as defined above

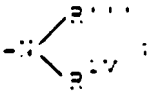
d'') a $-CH_2OCO(CH_2)_nCOOR_a$ or a $-NHCO(CH_2)_nCOOR_a$ group, wherein n and R_a are as defined above.

e'') a

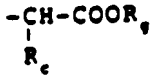


group, wherein R^{III} and R^{IV} are as defined above.

f'') a C_2-C_4 alkoxycarbonyl group substituted by a

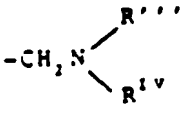


group, wherein R^{III} and R^{IV} are as defined above. Q represents hydrogen, C_2 or C_3 alkoxycarbonyl or a $-CONR^{'}_aR^{'}_b$ group wherein $R^{'}_a$ is hydrogen or C1-C_4 alkyl and $R^{'}_b$ is C1-C_4 alkyl, a



group wherein R_g and R_c are as defined above or a $-(CH_2)_p-R^{'}_5$ group in which p is zero, 1 or 2 and $R^{'}_5$ is:

a') unsubstituted pyridyl; or phenyl unsubstituted or substituted by one or two substituents chosen independently from nitro, halogen, CF_3, C1-C_4 alkyl, C1-C_4 alkoxy, CH_2OH, COOH, di(C_1 or C_2 alkyl) amino, hydroxy, formyloxy, C_2-C_6 alkanoyloxy and a



group wherein R^{III} and R^{IV} are as defined above;

b') 2-thienyl or 2-furyl; or

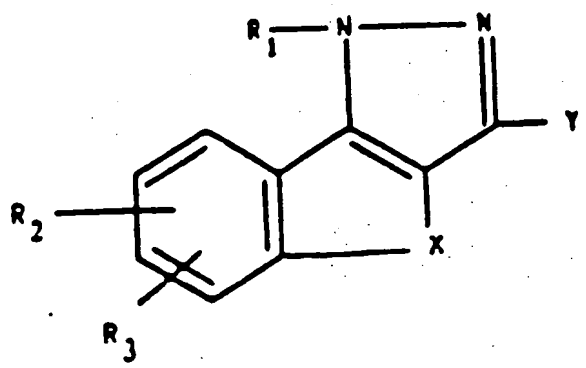
c') a heterocyclic ring which is selected from 2-thiazolyl or 3-isoxazolyl and which is unsubstituted or substituted by methyl; and the pharmaceutically acceptable salts thereof

Examples of particularly preferred compounds of the invention are

2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.
2-cyano-3-(7-fluoro-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-[1-(4-fluoro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-3-oxo-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-7-methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
N-(3-chloro-phenyl)-2-cyano-3-[1-(4-fluoro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-1-phenyl-indeno[1,2-c-]pyrazol-3-yl)-3-oxo-propanamide;
N-(3-chloro-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide.
2-cyano-3-(1,4-dihydro-4-methyl-1-phenyl-indeno[1,2-c]pyrazol3-yl)-3-oxo-N-phenyl-propanamide;
2-cyano-3-(1,4-dihydro-7-methyl-1-phenyl-indeno[1,2-c]pyrazol3-yl)-3-oxo-N-phenyl-propanamide;
N-[2-cyano-3-(1,4-dihydro-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-glycine,methyl ester.
N-[2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-glycine.
2-cyano-3-oxo-3-(1-phenyl-1H-benzothieno[3,2-c]pyrazol-3-yl)-N-phenyl-propanamide.
2-cyano-N-(4-fluoro-phenyl)-3-oxo-3-(1-phenyl-1H-benzothieno[3,2-c]pyrazol-3-yl-propanamide;

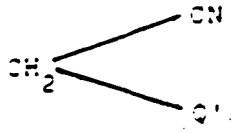
2-cyano-N-(4-fluoro-phenyl)-3-[1-(4-fluoro-phenyl)-1H-benzothieno[2,3-c]pyrazol-3-yl]-3-oxo-propanamide.
2-cyano-N-(4-fluoro-phenyl)-3-(7-fluoro-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide.
3-(7-amino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide.
2-cyano-3-(5-ethoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.
N-[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno[1,2-c]pyrazol-7-yl]carbonyl-glycine methyl ester;
2-cyano-3-(7-ethoxalyamino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.
2-cyano-3-(1,4-dihydro-7-N,N-dimethylaminoethoxycarbonyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide;
3-(7-tert.butyl-1,4-dihydro-1-phenyl-indeno[1,2,-c]pyrazol-3-yl)-2-cyano--N-(4-fluoro-phenyl)-3-oxo-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-1-phenyl-7-trifluoromethyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
and the pharmaceutically acceptable salts thereof, in particular the sodium and the potassium salts. The compounds of formula (I) and the salts thereof can be prepared by a process comprising:

a) reacting a compound of formula (II)



(II)

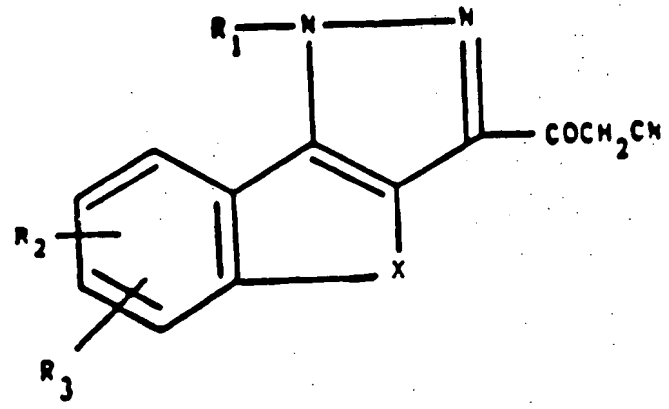
wherein
X, R_1, R_2 and R_3 are as defined above and Y is carboxy or a reactive derivative of a carboxy group, with a compound of formula (III)



(III)

wherein
Q' is as Q defined above, except carboxy, so obtaining a compound of formula (I), wherein Q is as defined above except carboxy; or

b) reacting a compound of formula (IV)



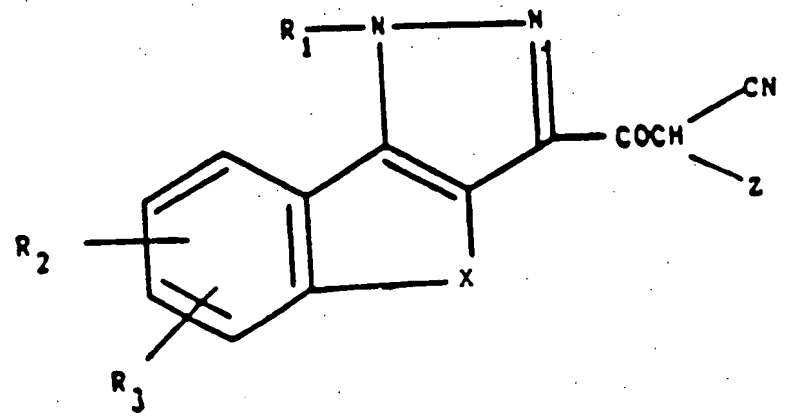
(IV)

wherein
X, R1, R2 and R3 are as defined above, with a compound formula (V)

R_b-N=C=O (V)

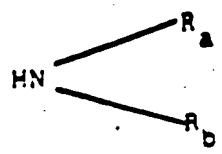
wherein
R_b is as defined above, so obtaining a compound of formula (I) wherein Q is a -CONHR$_b$ group, wherein R_b is as defined above; or

c) reacting a compound of formula (VI)



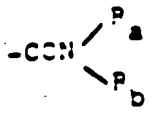
(VI)

wherein
X, R1, R2 and R3 are as defined above and Z is a reactive derivative of a carboxy group, with a compound of formula(VII)



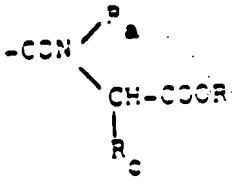
(VII)

wherein
R_a and R_b are as defined above, so obtaining a compound of formula (I) wherein Q is a



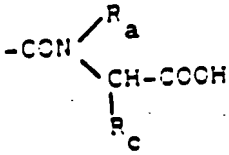
group, wherein R_a and R_b are as defined above, or

d) hydrolysing a compound of formula (I), wherein Q is a C_2-C_7 alkoxycarbonyl or



group in which R_a and R_c are as defined above and R is C_1-C_5 alkyl, so as to obtain the corresponding compound of formula (I), wherein

Q is a free carboxy group or a



group, in which R_a and R_c are as defined above; and, if desired, converting a compound of formula (I) into another compound of formula (I) and/or, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound, and/or, if desired, separating a mixture of isomers of a compound of formula (I), into the single isomers.

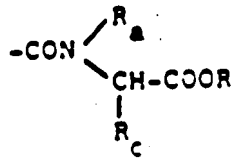
When Y is a reactive derivative of a carboxy group, it is, for example, a halocarbonyl group, preferably a chlorocarbonyl group, or a C_2-C_7 alkoxycarbonyl group, preferably a C_2-C_5 alkoxycarbonyl group.

The reaction between a compound of formula (II) wherein Y is carboxy and a compound of formula (III) may be carried out, for example, in the presence of a condensing agent such as diethyl cyanophosphonate, in the presence of a base such as triethylamine, in an inert solvent such as dimethylformamide, at a temperature varying between about 0°C and about 50°C. The reaction between a compound of formula (II) wherein Y is a reactive derivative of a carboxy group and a compound of formula (III) may be carried out, for example, in the presence of a strong base such as sodium hydride, potassium t-butoxide, thallous ethoxide, in an inert solvent such as 1,2-dimethoxyethane, dioxane, dimethylformamide, at a temperature varying between about 0°C and about 100°C.

The reaction between a compound of formula (IV) and a compound of formula (V) may be carried out, for example, in the presence of a base such as sodium hydride or triethylamine, in an inert solvent such as toluene, dioxane, tetrahydrofuran, dimethylformamide, at a temperature varying between about 0°C and about 100°C. In the compounds of formula (VI), Z is, for example, a halocarbonyl group, preferably a chlorocarbonyl group, or a C_2-C_7 alkoxycarbonyl group, preferably a C_2-C_5 alkoxycarbonyl group.

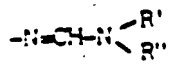
The reaction between a compound of formula (VI), wherein Z is a halocarbonyl group, and a compound of formula (VII) may be carried out, for example, in an inert solvent such as dichloroethane, dioxane, dimethylformamide, in the presence of pyridine or triethylamine as acid acceptor, at a temperature varying between about 0°C and about 100°C. The reaction between compound of formula (VI), wherein Z is C_1-C_5 alkyl ester, and a compound of formula (VII) may be carried out, for example, by heating at the reflux temperature in an aromatic hydrocarbon such as toluene or xylene, preferably distilling off slowly together with the diluent the free C_1-C_5 alkyl alcohol generated during the reaction.

Hydrolysis of a compound of formula (I), wherein Q is a C_2-C_7 alkoxycarbonyl group or a

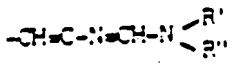


in which R_a and R_c are as defined above R is C_1-C_6 alkyl, according to process - variant d) above, may be performed by selective basic hydrolysis, using e.g. aqueous sodium or potassium hydroxide in a solvent such as dioxane,ethanol or dimethylformamide at a temperature varying between about 0°C and about 80°C.

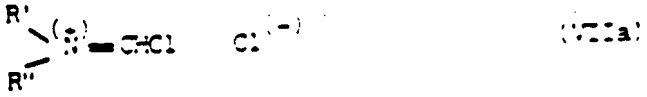
A compound of formula (I) may be converted, as stated above, into another compound of formula (I) by known methods; for example, in a compound of formula (I) a nitro group may be converted into an amino group by treatment, for example, with stannous chloride in concentrated hydrochloric acid, using, if necessary, an organic cosolvent such as acetic acid, dioxane, tetrahydrofuran at a temperature varying between room temperature and about 100°C Furthermore, for example, an amino group may be converted into a formylamino or a C_2-C_8 alkanoylamino group, for example by reacting with formic acid or with the suitable C_2-C_8 alkanoyl anhydride without any solvent or in an organic solvent such as dioxane, dimethylformamide, tetrahydrofuran, usually in the presence of a base such as pyridine or triethylamine, at a temperature varying between 0°C and about 100°C. Furthermore, for example, a $-NH_2$ or a $-CH=N-NH_2$ group may be converted into a



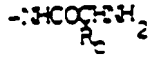
or into a



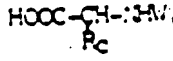
group, where R' and R'' are as defined above, respectively, by reaction with a quaternary nitrogen compound of formula (VIIa)



wherein R' and R'' are as defined above in an organic inert solvent, such as dioxane, tetrahydrofuran, chloroform, dichloromethane, 1,2-dichloroethane, benzene or toluene, in the presence of a tertiary amine, such as triethylamine, at a temperature varying between about -20°C and the room temperature, according to the experimental procedure described in British patent specification 1293590 and in U.S. patent 4,447,432. Furthermore, for example, an amino group may be converted into a

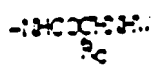


group, wherein R_c is as defined above, by reaction with a suitably protected aminoacid of formula

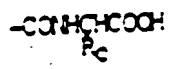


wherein R_c is as defined above and W is a protective group, such as a benzyloxycarbonyl or a tert-butoxycarbonyl group, in the presence of dicyclohexylcarbodiimide as condensing agent, in inert organic solvent such as dioxane, tetrahydrofuran or acetonitrile, at a temperature varying between about 0°C and

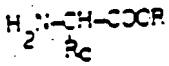
the room temperature so as to obtain the protected



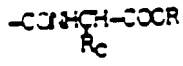
group, wherein R_c and W are as defined above, which in turn is deprotected using well known methods in organic chemistry. Furthermore, for example, a carboxy group may be converted into a



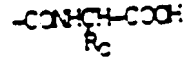
group, wherein R_c is as defined above, by reaction with an esterified α-aminoacid of formula



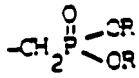
wherein R is C_1-C_4 alkyl and R_c is as defined above, in the presence of dicyclohexylcarbodiimide as condensing agent, in an inert organic solvent such as dioxane, tetrahydrofuran or acetonitrile, at a temperature varying between about 0 °C and the room temperature, so as to obtain the esterified



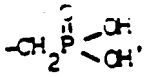
group, wherein R_c and R are as defined above, which in turn is hydrolized to yield the



group, wherein R_c is as defined above, following methods well known in the art, for example, those described for the process variant d) above. Furthermore, for example, an alkoxycarbonyl group, a



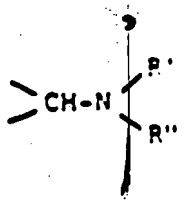
group, a $-CH_2OCO(CH_2)_nCOOR$ group or a $-NHCO(CH_2)_nCOOR$ group, wherein n is as defined above and R is C_1-C_4 alkyl may be converted into the corresponding -COOH,



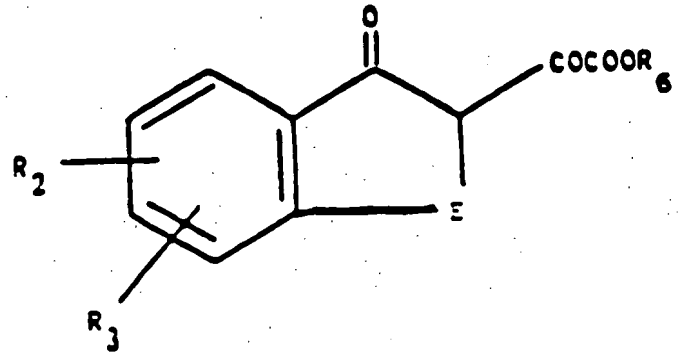
$-CH_2OCO(CH_2)_nCOOH$ and $-NHCO(CH_2)_nCOOH$ group, respectively, wherein n is as defined above, by treatment with aqueous sodium or potassium hydroxide in a solvent such as dioxane, methanol, ethanol or dimethylformamide, at a temperature varying between about 0 °C and about 80 °C.

The optional esterification of a free carboxy group as well as the optional conversion of a carboxylic ester into the free carboxy derivative may be carried out according to known methods in organic chemistry.

Process-variants b) and c) described above may be considered as examples of conversion of a compound of formula (I) into another compound of formula (I) too. Also the optional salification of a compound of formula (I) as well as the conversion of a salt into the free compound and the separation of a mixture of isomers into the single isomers may be carried out by conventional methods. For example, the separation of optical isomers may be carried out by salification with an optically active base or acid and by subsequent fractional crystallization of the diastereoisomeric salts, followed by recovering of the optically active isomeric acids or, respectively, bases. The compounds of formula (II), in which Y is a C_2-C_7 alkoxycarbonyl group and X, being as defined above, is other than a

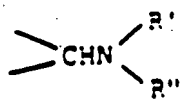


group, wherein R' and R'' are as defined above, may be prepared, for example, by reacting a compound of formula (VIII)



(VIII)

wherein
R_2 and R_3 are as defined above, E is as X defined above except a

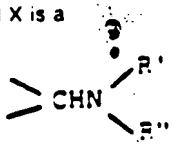


group, wherein R' and R'' are as defined above,and R_6 is C_1-C_4 alkyl, preferably C_1-C_2 alkyl, with a compound of formula (IX)

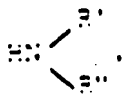
R_1-$NHNH_2$ (IX)

wherein
R_1 is as defined above.

The reaction between a compound of formula (VIII) and a compound of formula (IX) may be carried out, for example, in a solvent such as C_1-C_5 alkyl alcohol, dioxane, tetrahydrofuran, dimethylformamide, acetic acid, at a temperature varying between about 0° C and about 150° C. The compounds of formula (II), in which Y is a C_2-C_7 alkoxycarbonyl group and X is a



group, wherein R' and R'' are as defined above, may be prepared, for example, by reacting a compound of formula (II), wherein X is $=CH_2$, with an N-halosuccinimide, preferably N-bromosuccinimide, in an inert solvent such as carbon tetrachloride or chloroform, at a temperature varying from about 20° C to the reflux temperature, so obtaining the respective intermediate haloderivative of formula (II) in which X is a $=CH$-Halo group, in particular a $=CHBr$ group, which in turn is reacted with a compound of formula

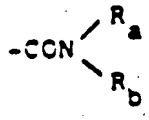


wherein R' and R'' are as defined above, in a solvent such as dimethylformamide, acetone, 2-butanone, in

the presence of sodium carbonate or potassium carbonate, at a temperature varying between about 0° C and about 100° C. The compounds of formula (II), wherein Y is carboxy may be prepared, for example, by hydrolysis of the corresponding compounds of formula (II) wherein Y is C_2-C_7 alkoxycarbonyl, according to standard methods well known in the art, for example by basic hydrolysis, carried out e.g. by treatment with sodium or potassium hydroxide in a solvent such as water, C_1-C_4 alkyl alcohol, dioxane, dimethylformamide and their mixtures, at a temperature varying between about 0° C and about 80° C.

The compounds of formula (II), wherein Y is halocarbonyl, preferably chlorocarbonyl, may be prepared, for example, by reaction of the corresponding compound of formula (II), wherein Y is carboxy, with the suitable acid halide, for example oxalyl chloride, thionyl chloride, PCl_3, PBr_3, in an inert solvent such as ether, benzene, dichloroethane, dioxane or without any solvent, at a temperature varying between about 0° C and about 100° C.

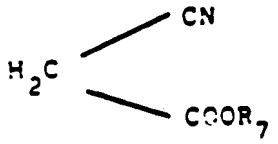
The compounds of formula (III) are, in some cases, commercially available products, or may be prepared by methods well known in the art. For example a compound of formula (III), wherein Q is a



group, wherein R_a and R_b are as defined above, may be prepared by reacting cyano-acetic acid with a compound of formula (VII) in the presence of a condensing agent such as dicyclohexylcarbodiimide, 1,1-carbonyldiimidazole and the like, in an inert organic solvent such as benzene, dioxane, acetonitrile, at a temperature varying between about 0° C and about 50° C.

The compounds of formula (IV) are compounds of general formula (I), wherein Q is hydrogen and may be obtained by process a) above, for example by reacting a compound of formula (II), wherein Y is C_2-C_7 alkoxycarbonyl, with acetonitrile, in the presence of a strong base e.g. sodium hydride, potassium tert.butoxide, in an inert organic solvent such as benzene, dioxane, tetrahydrofuran, at a temperature varying between about 0° C and about 100° C.

The compounds of formula (VI),wherein Z is C_2-C_7 alkoxycarbonyl, are compounds of general formula (I) wherein Q is C_2-C_7 alkoxycarbonyl and may be obtained by process a) above, for example, by reacting a compound of formula (II) with a compound of formula (X)

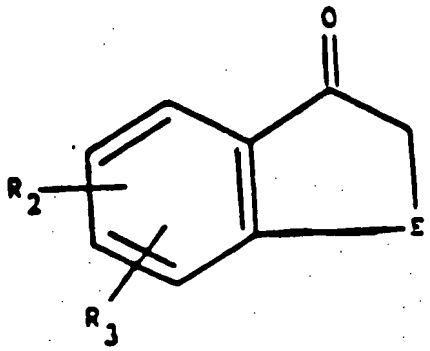


(X)

wherein
R_7 is C_1-C_6 alkyl, using the same experimental conditions as described above for the reaction between a compound of formula (II) and a compound of formula (III).

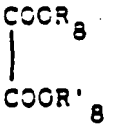
The compounds of formula (VI), wherein Z is halocarbonyl, may be prepared, for example, by basic hydrolysis of a compound of formula (VI), wherein Z is C_2-C_7 alkoxycarbonyl, using, for example, the same experimental conditions described above for the hydrolysis of the compounds of formula (II), wherein Y is C_2-C_7 alkoxycarbonyl, in order to obtain the corresponding carboxy derivative, which in turn may be transformed into a compound of formula (VI), wherein Z is halocarbonyl, preferably chlorocarbonyl, using, for example, the same experimental conditions described above for the preparation of the compounds of formula (II), wherein Y is halocarbonyl.

The compounds of formula (VIII) may be prepared, for example, by reacting a compound of formula (XI).



(XI)

wherein
E, R_2 and R_3 are as defined above, with a compound of formula (XII)



(XII)

wherein
each of R_8 and R'_8, being the same or different, is C_1-C_6 alkyl, preferably methyl or ethyl.
The reaction between a compound of formula (XI) and a compound of formula (XII) may be carried out, for example, according to the methods described in J.C.S., 101, 1731 (1912) and Ann., 405, 391 (1914).
The compounds of formula (XI) may be prepared by synthetic methods well known in the art, for example, according to the methods described in J.A.C.S., 75, 1891 (1953) and Advances in Heterocyclic Chemistry, 11, 225 (1970); ibidem 18, 432 (1975).
The compounds of formula (V), (VII), (IX), (X), and (XII) are known products and may be prepared by conventional methods: in some cases they are commercially available products.
When in the compounds of the present invention and in the intermediate products thereof, groups are present, such as CHO, COOH, NH_2 and/or OH, which need to be protected before submitting them to the hereabove illustrated reactions, they may be protected before the reactions take place and then deprotected, according to well known methods in organic chemistry.
The compounds of formula (I) possess immunomodulating activity and can be used for example as immunostimulant agents e.g. in the treatment of acute and chronic infections of both bacterial and viral origin, alone or in association with antibiotic agents, and in the treatment of neoplastic diseases, alone or in association with antitumoral agents, in mammals.
The immunomodulating activity of the compounds of the invention is proved, for example, by the fact that they are effective in potentiating the cytotoxic activity of the macrophages towards tumor cells in vitro. The experimental procedure to evaluate this activity is as follows: groups of 4 mice are treated i.p. with the tested compounds and then, seven days later, peritoneal cells are collected and plated for 2 hours at 37° C. After this period the walls are washed to eliminate the non adherent cells, tumor target cells are then added and the incubation prolonged for 48 hours. At the end of this period the target cells viability is evaluated by the MTT colorimetric method (Abstracts of VIII European Immunology Meeting, Zagreb, 1987, pag 94 n° 2105) based on the optical density (OD) evaluation at 570 nm
Percent specific cytotoxicity (%C) is calculated as % inhibition of TU-5 tumor cells (Immunology, 1984, 166, 251) growth using the following formula:

$$\%C = \left(1 - \frac{\text{effector + target OD} - \text{effector OD}}{\text{target OD}}\right) \cdot 100$$

The following Table I summarizes the immunostimulating activity data of some representative compounds of the invention, obtained according to hereabove experimental procedure, towards TU-5 tumor cells.

TABLE 1

EFFECT OF FCE 25276, FCE 25648, FCE 25651 and FCE 26047 ON THE CYTOTOXIC ACTIVITY OF PERITONEAL MACROPHAGES TOWARDS TU-5 TUMOR CELLS		
Compound	Effector Target	Macrophage cytotoxic activity (% inhibition of TU-5 growth) 10 mg kg i.p.
FCE 25276	5 : 1	93
FCE 25648	5 : 1	77
FCE 25651	5 : 1	79
FCE 26047	5 : 1	82
Vehicle	5 : 1	24
4 animals were used for each dose FCE 25276 means 2-cyano-3-(1,4-dihydro-1-phenyl-indeno [1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide. FCE 25648 means 2-cyano-3-(1,4-dihydro-1-phenyl-indeno [1,2-c]pyrazol-3-yl)-N-(4-fluoro-phenyl)-3-oxo-propanamide; FCE 25651 means N-(3-chloro-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno [1,2-c]pyrazol-3-yl)-3-oxo-propanamide; FCE 26047 means 2-cyano-3-oxo-3-(1-phenyl-1H-benzothieno [3,2-c]pyrazol-3-yl)-N-phenyl- propanamide		

By virtue of their immunomodulatory activity the compounds of the invention proved to be active also in models of infection in mice. For example, the compounds FCE 25276, FCE 25648, FCE 25651 and FCE 26047 are strongly effective against Pseudomonas aeruginosa infection, performed in Cyclophosphamide immunosuppressed mice according to Cryz S. J. et al., Infect. Imm., 1983, 39, 1067

The experimental procedure to evaluate this activity is as follows: mice are immunosuppressed 4 days before the bacterial challenge by a single dose of 200 mg/kg of Cyclophosphamide given intraperitoneally. Tested compounds are administered i.p. on days + 1 and + 3 relative to Cyclophosphamide administration. Clinically isolated Pseudomonas aeruginosa is administered intravenously in amount of 8 LD_{50}. Host resistance to infection is estimated by the number of mice surviving 10 days after the bacterial challenge.

The following Table 2 summarizes the obtained results.

TABLE 2

EFFECT OF FCE 25276, FCE 25648, FCE 25651 AND FCE 26047 ON PSEUDOMONAS AERUGINOSA INFECTION IN CYCLOPHOSPHAMIDE IMMUNO-DEPRESSED MICE		
Compound	treatment	% survival 8 LD_{50}
FCE 25276	10 mg kg i.p.	90
FCE 25648	10 mg kg i.p.	90
FCE 25651	10 mg kg i.p.	90
FCE 26047	10 mg kg i.p.	70
Vehicle	---------	0
10 animals were used for each dose		

The compounds of the invention can be safely used in medicine by virtue of their negligible toxicity. The therapeutic regimen for the different clinical syndromes must be adapted to the type of pathology

taking into account as usual also the route of administration the form in which the compound is administered and the age weight and conditions of the subject involved The oral route is employed in general for all conditions requiring such compounds Preference is given to intravenous injection or infusion for the treatment of acute infections For maintenance regimens the oral or parenteral e g intramuscular or subcutaneous route is preferred

For these purposes the compounds of the invention e g 2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2]-pyrazol-3-yl) -3-oxo-N-phenyl-propanamide can be administered orally at doses ranging e g from about 0 5 to about 10 mg kg of body weight per day in adult humans

Doses of active compounds ranging e g from about 0.2 to about 5 mg kg of body weight can be used for the parenteral administration in adult humans. Of course, these dosage regimens may be adjusted to provide the optimal therapeutic response.

The nature of the pharmaceutical compositions containing the compounds of this invention in association with pharmaceutically acceptable carriers or diluents will, of course, depend upon the desired route of administration The compositions may be formulated in the conventional manner with the usual ingredients

For example, the compounds of the invention may be administered in the form of aqueous or oily solutions or suspension tablets, pills, gelatine capsules, syrups, drops or suppositories. Thus, for oral administration, the pharmaceutical compositions containing the compounds of this invention, are preferably tablets, pills or gelatine capsules which contain the active substance together with diluents, such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubricants, for instance silica, talc, stearic acid, magnesium or calcium stearate, and or polyethylene glycols; or they may also contain binders, such as starches, gelatine, methylcellulose, carboxymethylcellulose, gum-arabic, tragacanth, polyvinylpyrrolidone; disaggregating agents, such as starches, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and phamacologically inactive substances used in pharmaceutical formulations.

Said pharmaceutical preparations may be manufactured in known manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes. The liquid dispersions for oral administration may be e g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and or mannitol and or sorbitol. The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspensions or solutions for intramuscular injections may contain together with the active compound a pharmaceutically acceptable carrier, e.g sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride The solutions for intravenous injections or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile aqueous isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin

The following examples illustrate but do not limit the invention

Example 1

2-Ethoxalyl-indan-1-one(6 g) is reacted with phenylhydrazine (3 1 g) in acetic acid 45 ml) at 50°C for 3 hours After cooling the reaction mixture is diluted with ice water and then neutralized with 35% NaOH Extraction with ethyl acetate and evaporation of the solvent in vacuo to dryness gives a residue which is purified over a SiO_2 column using hexane chloroform 6 4 as eluent Main fractions are crystallized from isopropyl ether to yield 1,4-dihydro-1-phenyl-indeno[1,2-c] pyrazole-3-carboxylic acid, ethyl ester, m p 110-112°C (5.7 g), which is reacted with acetonitrile (14 ml) in dioxane (14 ml) in the presence of 50% sodium hydride (0 9 g) under stirring at 60°C for 15 minutes After cooling the reaction mixture is diluted with ice water and acidified to pH 4 with citric acid The precipitate is filtered and purified over a SiO_2 column using ethyl acetate as eluent Crystallization from dichloromethane isopropyl alcohol gives 3-(1 4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanenitrile m p 189-190°C (2 8 g), which is reacted with phenyl isocyanate (1 17 g) in dimethylformamide (22 ml) in the presence of triethylamine (1 06 g) at 25-30°C for 25 minutes The reaction mixture is diluted with ice water and acidified with 2N HCl to pH 3 The precipitate is filtered and washed with water Crystallization from dichloromethane methanol gives 3 5 g of 2-cyano-3-(1,4-dihydro 1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide m p 273-277°C NMR (CDCl$_3$)δppm 3 91(s) (2H C-4 protons) 7 1-8 0(m) (15H Phenyl protons and -CONH-) 16 2 (bs) (1H -OH)

By proceeding analogously the following compounds can be prepared

2-cyano-3-[1-(4-fluoro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-3-oxo-N-phenyl-propanamide.
3-[1-(4-chloro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-2-cyano-3-oxo-N-phenyl-propanamide.
3-[1-(3-chloro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-2-cyano-3-oxo-N-phenyl-propanamide.
3-[1-(2-chloro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-2-cyano-3-oxo-N-phenyl-propanamide.
2-cyano-3-[1-(3-fluoro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-3-oxo-N-phenyl-propanamide;
2-cyano-3-[1,4-dihydro-1-(4-methyl-phenyl)-indeno[1,2-c]pyrazol-3-yl]-3-oxo-N-phenyl-propanamide;
2-cyano-3-[1,4-dihydro-1-(3-methyl-phenyl)-indeno[1,2-c]pyrazol-3-yl]-3-oxo-N-phenyl-propanamide;
2-cyano-3-[1,4-dihydro-1-(2-methyl-phenyl)-indeno[1,2-c]pyrazol-3-yl]-3-oxo-N-phenyl-propanamide;
2-cyano-3-[1,4-dihydro-1-(4-methoxy-phenyl)-indeno[1,2-c]pyrazol-3-yl]-3-oxo-N-phenyl-propanamide.
2-cyano-3-[1,4-dihydro-1-(3-methoxy-phenyl)-indeno[1,2-c]pyrazol-3-yl]-3-oxo-N-phenyl-propanamide.
2-cyano-3-[1,4-dihydro-1-(4-nitro-phenyl)-indeno[1,2-c]pyrazol-3-yl]-3-oxo-N-phenyl-propanamide.
2-cyano-3-[1,4-dihydro-1-(3-nitro-phenyl)-indeno[1,2-c]pyrazol-3-yl]-3-oxo-N-phenyl-propanamide. and
2-cyano-3-(1,4-dihydro-1-methyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.

Example 2

By proceeding according to Example 1 using the suitable isocyanates, the following compounds can be prepared:
N-(3-chloro-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide, m.p.269-271 °C.
N-(4-chloro-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
N-(2-chloro-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide, m.p.295-297 °C;
2-cyano-N-(3-fluoro-phenyl)-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-(3-trifluoromethyl-phenyl)-propanamide, m.p.278-284 °C;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(4-methyl-phenyl)-3-oxo-propanamide.
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(3-methyl-phenyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(2-methyl-phenyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(4-methoxy-phenyl)-3-oxo-propanamide.
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(3-methoxy-phenyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(3-nitro-phenyl)-3-oxo-propanamide, m.p.280-284 °C.
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(4-nitro-phenyl)-3-oxo-propanamide;
N-(3-bromo-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-oxo-propanamide;
N-benzyl-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c] pyrazol-3-yl)-3-oxo-propanamide, m.p. 289-290 °C.
N-benzyl-2-cyano-3-[1-(1-(4-fluoro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-3-oxo-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-[1-(4-fluoro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-3-oxo-propanamide,m.p.281-286 °C de
N-(3-chloro-phenyl)-2-cyano-3-[1-(4-fluoro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-3-oxo-propanamide, m.p.288-291 °C.
N-butyl-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide and
N-tert.butyl-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide

Example 3

By proceeding according to Examples 1 and 2, starting from suitable indan-1-ones, the following compounds can be prepared
2-cyano-3-(1,4-dihydro-4-methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide
2-cyano-3-(1,4-dihydro-5-methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.
2-cyano-3-(1,4-dihydro-6-methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.
2-cyano-3-(1,4-dihydro-7-methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide,m.p. 249-251 °C.
3-(5-chloro-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide.
3-(6-chloro-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide
3-(7-chloro-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide

2-cyano-3-(7-fluoro-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide m.p. 259-263° C
2-cyano-3-(1,4-dihydro-5-methoxy-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.
2-cyano-3-(1,4-dihydro-7-dimethylamino-1-phenyl-indeno[1,2-c]pyrazol-3-yl)3-oxo-N-phenyl-propanamide
2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-1-phenyl-7-trifluoromethyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide.
N-(3-chloro-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-7-trifluoromethyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide.
N-(3-chloro-phenyl)-2-cyano-3-(7-fluoro-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide.
3-(7-tert.butyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide.
3-(7-tert.butyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-N-(4-fluoro-phenyl)-3-oxo-propanamide.
2-cyano-3-(1,4-dihydro-7-morpholinomethyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.
2-cyano-3-(1,4-dihydro-6-morpholinomethyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.
2-cyano-3-(1,4-dihydro-5-morpholinoemethyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.
N-(3-chloro-phenyl)-2-cyano-3-(1,4-dihydro-7-methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-7-methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-(7-fluoro-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl-3-oxo-propanamide;
and
2-cyano-3-(1,4-dihydro-1-phenyl-7-trifluoromethyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.

Example 4

1,4-Dihydro-1-phenyl-indeno[1,2-c]pyrazole-3-carboxylic acid, ethyl ester (7.35 g), prepared according to Example 1, is dissolved in carbon tetrachloride (100 ml) and reacted with N-bromo-succinimide (4.75 g) under stirring at the reflux temperature for 2 hours, in the presence of benzoyl peroxide (150 mg). After cooling the reaction mixture is filtered and the solution is evaporated in vacuo to a small volume. The precipitated product is purified with hot isopropyl ether to give 4-bromo-1,4-dihydro-1-phenyl-indeno [1,2-c]-pyrazole-3-carboxylic acid,ethyl ester, m.p. 181 - 182° C (9.2g) which is reacted with morpholine (2.5 g) in dimethylformamide (175 ml), in the presence of anhydrous potassium carbonate, under stirring at room temperature for 2 hours. The reaction mixture is diluted with ice water and the precipitate is filtered and washed with water until neutral. Crystallization from dichloromethane - isopropyl ether gives 1,4-dihydro-4-morpholino-1-phenyl-indeno[1,2-c]pyrazole-3-carboxylic acid, ethyl ester m.p. 150-151° C (5.4 g), which is hydrolized by treatment with 1% KOH in 95% ethanol solution (93 ml) at the reflux temperature for 20 minutes. After cooling the reaction mixture is diluted in ice water and acidified with citric acid to pH 4. The precipitate is filtered, washed with water until neutral and crystallized from dichloromethane ethanol to yield 1,4-dihydro-4-morpholino-1-phenyl-indeno[1,2-c]pyrazole-3-carboxylic acid m.p. 244-245° C (4.15 g), which is reacted with thionyl chloride (1.65 ml) in dioxane (200 ml) at the reflux temperature for 1 hours. After cooling the reaction mixture is evaporated to dryness in vacuo to give 1,4-dihydro-4-morpholino-1-phenyl-indeno[1,2-c]pyrazole-3- carbonyl chloride as crystalline residue. The crude product is dissolved in anhydrous dioxane (300 ml) and reacted for 2 hours under stirring at room temperature with the carbanion obtained by treatment of 2-cyano-acetanilide (1.87 g) with 50% sodium hydride (1.2 g) in anhydrous dioxane (100 ml) at room temperature. The reaction mixture is neutralized by treatment with N HCl (7 ml) and then concentrated in vacuo to a small volume.
The residue is diluted with ice water and acidified with N HCl to pH 4. The precipitate is filtered, washed with water and then crystallized from dimethylformamide to give 2.2 g of 2-cyano-3-(1,4-dihydro-4-morpholino-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide m.p. 272-277° C dec.
By proceeding analogously the following compounds can be prepared:
2-cyano-3-(1,4-dihydro-1-phenyl-4-piperidino-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide
2-cyano-3-(1,4-dihydro-1-phenyl-4-(pyrrolidin-1-yl)-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide
2-cyano-3-[1,4-dihydro-4-(4-methyl-piperazin-1-yl)-1-phenyl-indeno[1,2-c]pyrazol-3-yl]-3-oxo-N-phenyl-propanamide.
2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-4-morpholino-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide.and

N-(3-chloro-phenyl)-2-cyano-3-(1,4-dihydro-4-morpholino-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide

Example 5

1,4-Dihydro-1-phenyl-indeno[1,2-c]pyrazole-3-carboxylic acid ethyl ester (3 g), prepared according to Example 1, is heated with 1% KOH solution in ethanol (100 ml) at reflux temperature for 20 minutes. The reaction mixture is diluted with ice water and acidified to pH 3 with 37% HCl. The precipitate is filtered, washed with water until neutral and dried in vacuo to give 1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazole-3-carboxylic acid (2.5 g) which is reacted with thionyl chloride (1.2 ml) in dioxane (60 ml) at the reflux temperature for 2 hours. After cooling the reaction mixture is evaporated to dryness in vacuo to give 1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazole-3-carbonyl chloride as crystalline residue. The crude product is dissolved in anhydrous dioxane (30 ml) and reacted for 2 hours under stirring at room temperature with the carbanion obtained by treatment of 2-cyano-acetanilide (1.6 g) with 50% sodium hydride (0.5 g) in anhydrous dimethylformamide dioxane 1:1 (10 ml) at room temperature. The reaction mixture is then diluted with ice water and acidified to pH 2 with HCl. The precipitate is filtered and washed with water until neutral. Crystallization from dichloromethane methanol gives 1.6 g of 2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]-pyrazol-3-yl)-3-oxo-N-phenyl-propanamide, m.p. 273-277° C.

By proceeding analogously the following compounds can be prepared:
2-cyano-N-(4-fluoro-benzyl)-3-(1,4-dihydro-1-phenyl-indeno [1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-(2-pyridyl)methyl-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-(3-pyricyl)-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenethyl-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(4-dimethylamino-phenyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(2-morpholinomethyl-benzyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(3-morpholinomethyl-benzyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(2-morpholinomethyl-phenyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(3-morpholinomethyl-phenyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(3-dimethylaminomethyl-phenyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(3-hydroxy-4-hydroxymethyl-phenyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(2-dimethylaminomethyl-phenyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl-3-oxo-N-[2-(pyrrolidin-1-yl)methyl-phenyl]-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-[2-(4-methyl-piperazin-1-yl)methyl-phenyl]-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(2-methoxy-3-morpholinomethyl-phenyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(2-methoxy-5-morpholinomethyl-phenyl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-methyl-3-oxo-N-phenyl-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-(2-thenyl)-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(4-methoxy-3-morpholinomethyl-phenyl)-3-oxo-propanamide;
2-cyano-N-(2-furfuryl)-3-(1,4-dihydro-1-phenyl-indeno [1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(1-methyl-pyrrol-2-yl)ethyl-3-oxo-propanamide;
2-cyano-3-oxo-3-(1-phenyl-1H-benzothieno[3,2-c]pyrazol-3-yl)-N-phenyl-propanamide, m.p. 288-291° C.
2-cyano-N-(4-fluoro-phenyl)-3-oxo-3-(1-phenyl-1H-benzothieno [3,2-c]pyrazol-3-yl)-propanamide and
N-(3-chloro-phenyl)-2-cyano-3-oxo-3-(1-phenyl-1H-benzothieno [3,2-c]pyrazol-3-yl)-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-[1-(4-fluoro-phenyl)-1H-benzothieno[3,2-c]pyrazol-3-yl]-3-oxo-propanamide

Example 6

Ethyl cyanoacetate (1.4 g) is treated with 50% sodium hydride (0.58 g) in anhydrous dioxane (20 ml) under stirring at room temperature until the effervescence subsides. To this solution 1,4-dihydro-1-phenyl-indeno [1,2-c]pyrazole-3-carbonyl chloride (3 g), prepared according to Example 5 dissolved in anhydrous dioxane (50 ml) is added under stirring at room temperature. The reaction mixture is allowed to react for 20 hours, then it is diluted with ice water and acidified to pH 3 with 37% HCl. The precipitate is extracted with ethyl acetate and the organic solution washed with water and then evaporated to dryness in vacuo. The residue is purified over a SiO_2 column, using hexane-ethyl acetate 80:20 as eluent, to give 2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoic acid, ethyl ester (2.2 g), which is reacted with aniline (3.4 g) in xylene (100 ml) at the reflux temperature for 48 hours. After cooling the precipitate is filtered and washed with xylene, then crystallized from dichloromethane-methanol to give 1.2 g of 2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide, m.p. 273-277° C.

Example 7

1,4-Dihydro-1-phenyl-indeno[1,2-c]pyrazole-3-carbonyl chloride (2.3 g), prepared according to Example 5, is dissolved in anhydrous dioxane (35 ml) and reacted for 2 hours under stirring at room temperature with the carbanion obtained by treatment of N-cyanoacetyl-glycine, methyl ester (1.45 g) with 50% sodium hydride (0.54 g) in anhydrous dimethylformamide-dioxane 1:1 (30 ml) at room temperature. The reaction mixture is then diluted with ice water and acidified to pH 3 with 2N HCl.
The precipitate is filtered and dissolved in ethyl acetate, then the organic solution is washed with N HCl and then with water until neutral. Evaporation to dryness yields a residue which is purified over a Flash column using chloroform:methanol:30% NH_4OH 85:15:0.5 as eluent. Final treatment with acetone of the purified fractions gives 1.5 g of N-[2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-glycine, methyl ester, m.p.253-255° C.

By proceeding analogously the following compounds can be prepared:
N-[2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-DL-leucine, methyl ester;
N-[2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-DL-phenylalanine, methyl ester;
N-[2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-DL-phenylglycine, methyl ester; and
N-[2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-DL-isoleucine, methyl ester.
Similarly the pure D and L enantiomers of the above-listed compounds can be prepared.

Example 8

N-[2-Cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-glycine, methyl ester (1.7 g), is suspended in 1% KOH solution in 95% ethanol (60 ml) and heated under stirring at the reflux temperature for 30 minutes. After cooling the precipitate is filtered and washed with ethanol, then dissolved in water. The aqueous basic solution is extracted with ethyl acetate and then acidified to pH 3 with 2N HCl. The precipitate is extracted with ethyl acetate and the organic solution washed with N HCl and then with water until neutral. Evaporation to dryness in vacuo gives a residue which is crumbled with ethanol to yield 1.2 g of N-[2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-glycine, m.p. 247-249° C dec.

By proceeding analogously the following compounds can be prepared:
N-[2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-DL-leucine,
N-[2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-DL-phenylalanine,
N-[2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-DL-phenylglycine, and
N-[2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanoyl]-DL-isoleucine.
Similarly the pure D and L enantiomers of the above-listed compounds can be prepared.

Example 9

2-Cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(3-methoxyphenyl)-3-oxo-propanamide (4.5 g)

is treated with $SnCl_2$ $2H_2O$ (22.5 g) in 37% HCl (16 ml) and acetic acid (144 ml) under stirring at 50° C for 5 hours. After cooling the precipitate is filtered and washed with acetic acid, then dissolved in dimethylformamide 2N NaOH 1 l. Dilution with excess aqueous NaH_2PO_4 gives a precipitate which is filtered, washed with water and crystallized from dimethylformamide to yield 2.3 g of N-(3-amino-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide

By proceeding analogously the following compounds can be prepared

N-(4-amino-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno [1,2-c]pyrazol-3-yl)-3-oxo-propanamide; and

3-[1-(4-amino-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-2-cyano-3-oxo-N-phenyl-propanamide

Example 10

N-(3-Amino-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno [1,2-c]pyrazol-3-yl)-3-oxo-propanamide (1.8 g) dissolved in dimethylformamide (30 ml) is reacted with acetic anhydride (5 ml) in the presence of pyridine (5 ml) at 40° C for 8 hours. The reaction mixture is diluted with ice water and the precipitate is filtered and washed with water crystallization from dimethylformamide gives 1.2 g of N-(3-acetylamino-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c] pyrazol-3-yl)-3-oxo-propanamide

By proceeding analogously the following compounds can be prepared

N-(4-acetylamino-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide.

and

3-[1-(4-acetylamino-phenyl)-1,4-dihydro-indeno[1,2-c] pyrazol-3-yl]-2-cyano-3-oxo-N-phenyl-propanamide

Example 11

2-Cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide is dissolved by treatment with the stoichiometric amount of sodium ethoxide in ethanol. The solution is evaporated to dryness in vacuo and the product is crumbled with acetone. Filtration and washing with acetone gives the pure sodium salt of 2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide, m.p. > 300° C.

By proceeding analogously the sodium salts of the following compounds can be prepared.

2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-1-phenyl-indeno [1,2-c]pyrazol-3-yl)-3-oxo-propanamide;

2-cyano-N-(4-fluoro-phenyl)-3-[1-(4-fluoro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-3-oxo-propanamide;

2-cyano-N-(4-fluoro-phenyl)-3-(7-fluoro-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;

2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-7-methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide

Example 12

By proceeding according to Example 5, starting from suitable tert-butoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c] pyrazole-3-carboxylic acid ethyl esters, the following compound can be prepared

3-(5-tert-butoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide, m.p. 253-255 ° C.

3-(5-carboxy-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide, m.p. 265-268° C dec;

3-(7-carboxy-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-N-(4-fluoro-phenyl)-3-oxo-propanamide;

3-(7-carboxy-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-N-(3-chloro-phenyl)-2-oxo-propanamide;

3-(7-tert-butoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide; and

3-(7-carboxy-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide

Example 13

3-(5-Carboxy-1,4-dihydro-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide (2.3 g) dissolved in dimethylformamide (25 ml) is reacted with ethyl iodide (1.55 g) in the presence of anhydrous

potassium carbonate (1.4 g) under stirring at room temperature for 2 hours. The reaction mixture is diluted with ice water and the precipitate is filtered, dissolved in chloroform and washed with 1N HCl and then with water. Evaporation of the solvent in vacuo gives a residue which is crystallized from CH_2Cl_2 methanol to yield 1.9 g of 2-cyano-3-(5-ethoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide, **m.p. 233-236°C dec.**

By proceeding analogously the following compounds can be prepared
2-cyano-3-(7-ethoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide;
2-cyano-3-(7-hexyloxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide;
2-cyano-3-(7-ethoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(4-fluoro-phenyl)-3-oxo-propanamide; and
N-(3-chloro-phenyl)-2-cyano-3-(7-ethoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide.

Example 14

Glycine methyl ester hydrochloride (0.7 g) suspended in anhydrous acetonitrile (250 ml) is treated with triethylamine (0.56 g) under stirring at room temperature. To the suspension first 3-(7-carboxy-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide (2.3 g) and then dicyclohexylcarbodiimide (1.25 g) are added. The reaction mixture is kept under stirring at room temperature for 4 hours and then is basified to pH 8 by adding dimethylaminoethanol. The precipitate is filtered, washed with acetonitrile and then eliminated. The organic solution is concentrated in vacuo to a small volume, diluted with water, acidified to pH 2 with 1N HCl and then basified to pH 8 with 1N NaOH. The obtained precipitate is filtered, washed with water, dissolved in chloroform and washed with 1N HCl and then with water until neutral. The organic solution is evaporated in vacuo to dryness and the residue is purified over a SiO_2 column using $CHCl_3$ methanol 90:10 as eluent. Final crystallization from CH_2Cl_2 ethyl acetate yields 1.2 g of pure N-[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno[1,2-c]pyrazol-7-yl]carbonyl-glycine methyl ester.

By proceeding analogously the following compounds can be prepared:
N-[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)- indeno[1,2-c]pyrazol-7-yl]carbonyl-L-alanine methyl ester;
N-[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno[1,2-c]pyrazol-7-yl]carbonyl-L-leucine methyl ester;
N-[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno[1,2-c]pyrazol-7-yl]carbonyl-L-phenylalanine methyl ester;
N-{ 3-[2-(4-fluorophenylcarbamoyl)-cyanoacetyl]-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-7-yl} carbonyl-glycine methyl ester; and
N-[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno[1,2-c]pyrazol-5-yl]carbonyl-glycine methyl ester.

Example 15

N-[1,4-Dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno[1,2-c]pyrazol-7-yl]carbonyl-glycine methyl ester (0.85 g) is suspended in 1 % KOH solution in 95 % ethanol (22.3 ml) and heated under stirring at the reflux temperature for 30 minutes. After cooling the reaction mixture is acidified to pH 2 with 23 % HCl and then diluted with ice water. The precipitate is filtered, washed with water and then crystallized from CH_2Cl_2 ethanol to yield 0.65 g of pure N[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno-[1,2-c]pyrazol-7-yl]carbonyl glycine.

By proceeding analogously the following compounds can be prepared
N-[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno[1,2-c]pyrazol-7-yl]carbonyl-L-alanine
N-[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno[1,2-c]pyrazol-7-yl]carbonyl-L-leucine.
N-[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno[1,2-c]pyrazol-7-yl]carbonyl-L-phenylalanine.
N-{3-[2-(4-fluorophenylcarbamoyl)-cyanoacetyl]-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-7-yl}carbonyl-glycine, and

N-[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno[1,2-c]pyrazol-5-yl]carbonyl- glycine

Example 16

6-Tosylamino-indan-1-one, m.p. 202-204°C (4.2 g) is reacted with diethyl oxalate (20.5 g) in anhydrous ethanol (125 ml) containing sodium ethoxide (3.5 g) under stirring in inert atmosphere at room temperature for 2 hours. The reaction mixture is diluted with ice water and extracted with hexane. The aqueous phase is acidified to pH 3 with N HCl and extracted with ethyl acetate. The organic solution is washed with water until neutral and then is evaporated to dryness in vacuo to give crude 2-ethoxalyl-6-tosylamino-indan-1-one which is reacted with phenylhydrazine (1.65 g) in acetic acid (60 ml) at 60°C for 2 hours. The reaction mixture is diluted with ice water and the precipitate is filtered, washed with water, dissolved in $CHCl_3$ and evaporated to dryness in vacuo. Purification over a SiO_2 column using hexane-ethyl acetate 7:3 as eluent yields pure 1,4-dihydro-1-phenyl-7- tosylamino-indeno[1,2-c]pyrazole-3-carboxylic acid, ethyl ester (3.3 g), which is reacted with acetonitrile (12 ml) in anhydrous dioxane (50 ml) in the presence of 50 % sodium hydride (1.1 g) under stirring at 60°C for 4 hours. After cooling the reaction mixture is diluted with ice water and acidified to pH 4 with citric acid. The precipitate is extracted with ethyl acetate, washed with 5 % $NaHCO_3$ aqueous solution and then with water. By concentration to a small volume in vacuo the product crystallizes. The precipitate is filtered and washed with ethyl acetate to yield pure 3-(1,4-dihydro-1-phenyl-7-tosylamino-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanenitrile (2.1 g), which is reacted with phenyl isocyanate (0.55 g) in dimethylformamide (15 ml) in the presence of triethylamine (0.65 ml) at room temperature for 30 minutes. The reaction mixture is diluted with ice water and acidified to pH 2 with 2N HCl. The precipitate is filtered and washed with water until neutral. Crystallization from chloroform-ethanol yields 2-cyano-3-(1,4-dihydro-1-phenyl-7-tosylamino-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide (2.3 g), which is treated with methanesulphonic acid (11 ml) in the presence of anisole (1.3 ml) under stirring at 50°C for 20 hours. After cooling the reaction mixture is diluted with ice water and the precipitate is filtered and washed with water until neutral. Crystallization from CH_2Cl_2-methanol yields 1.2 g of 3-(7-amino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide.

By proceeding analogously the following compounds can be prepared:

3-(5-amino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-N-(4-fluoro-phenyl)-3-oxo-propanamide;
3-(7-amino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-N-(4-fluoro-phenyl)-3-oxo-propanamide;
3-(7-amino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(3-chloro-phenyl)-2-cyano-3-oxo-propanamide; and
3-(7-amino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-N-(3-trifluoromethyl-phenyl)-3-oxo-propanamide.

Example 17

3-(7-Amino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide (1.1 g) dissolved in anhydrous dimethylformamide (70 ml) containing pyridine (1 ml) is reacted with ethyl oxalyl chloride (0.7 g) under stirring at room temperature for 6 hours. The reaction mixture is diluted with ice water and acidified to pH 4 with citric acid. The precipitate is filtered and washed with water. Crystallization from $CHCl_3$-ethanol yields 1.1 g of 2-cyano-3-(7-ethoxalylamino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.

By proceeding analogously the following compounds can be prepared:

2-cyano-3-(5-ethoxalylamino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.
2-cyano-3-(7-ethoxalyamino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-N-(4-fluoro-phenyl)-3-oxo-propanamide; and
N-(3-chloro-phenyl)-2-cyano-3-(7-ethoxalylamino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide.

Example 18

2-Cyano-3-(7-ethoxalylamino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide (1.1 g) is treated with 1 % KOH solution in 95 % ethanol (34 ml) diluted with 95 % ethanol (50 ml) under stirring at room temperature for 3 hours. The reaction mixture is concentrated in vacuo to a

small volume and then diluted with ice water and acidified to pH 4 with citric acid. The precipitate is filtered and washed with water. Crystallization from $CHCl_3$-ethanol yields 0.65 g of 2-cyano-3-(1,4-dihydro-7-oxalamino-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.

By proceeding analogously the following compounds can be prepared:

2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-7-oxalamino-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;

N-(3-chloro-phenyl)-2-cyano-3-(1,4-dihydro-7-oxalamino-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide, and

2-cyano-3-(1,4-dihydro-5-oxalamino-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.

Example 19

3-(7-Amino-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide (1 g) dissolved in anhydrous tetrahydrofuran (23 ml) is reacted with succinic anhydride (0.71 g) at the reflux temperature under stirring for 3 hours. After cooling the reaction mixture is diluted with ice water. The precipitate is filtered and washed with water. Crystallization from $CHCl_3$-methanol yields 0.75 g of 3-[7-(3-carboxy-propanoylamino)-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide.

By proceeding analogously the following compounds can be prepared:

3-[5-(3-carboxy-propanoylamino)-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide; and

3-[7-(2-carboxyacetylamino)-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl]-2-cyano-3-oxo-N-phenyl-propanamide.

Example 20

5-Tert-butoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazole-3-carboxylic acid ethyl ester (11 g), prepared according to Example 16, is treated under stirring with trifluoroacetic acid (130 ml) at room temperature for 3 hours. The reaction mixture is diluted with ice water and the precipitate is filtered and washed with water until neutral. Crystallization from isopropanol yields 3-ethoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazole 5°carboxylic acid (8.4 g), which is reacted with thionyl chloride (5.3 ml) in anhydrous dioxane (90 ml) at the reflux temperature for 2 hours. After cooling the solution is evaporated to dryness in vacuo and the residue, 3-ethoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazole-5-carbonyl chloride, is dissolved in anhydrous diglyme (100 ml) and added dropwise, under inert atmosphere, to a stirred solution of lithium tri-tert-butoxyaluminum hydride (15.4 g) in anhydrous diglyme (90 ml) in such a way as to maintain the temperature between 0° C and 4° C. The reaction mixture is allowed to react at about 0° C under stirring for 1 hour and then is diluted with ice water, acidified to pH 1 with 23 % HCl and extracted with chloroform. The organic solution is washed with water and then evaporated to dryness in vacuo. The residue is purified over a SiO_2 column using hexane-ethyl acetate 7:3 as eluent. Crystallization from CH_2Cl_2-isopropyl ether yields pure 1,4-dihydro-5-hydroxymethyl-1-phenyl-indeno[1,2-c]pyrazole-3-carboxylic acid ethyl ester (3.8 g), which is reacted with 2-methoxyethoxymethyl chloride (2.1 g) in methylene chloride (60 ml) in the presence of diisopropylethylamine (2.96 ml) at room temperature for 20 hours. The reaction mixture is washed in a separatory funnel first with 5 % Na_2HPO_4 solution and then with water until neutral. The organic phase is evaporated to dryness in vacuo and the residue is crystallized from isopropyl ether to yield 1,4-dihydro-5-(2-methoxyethoxymethoxy)methyl-1-phenyl-indeno[1,2-c]pyrazole-3-carboxylic acid ethyl ester (4.65 g), which is treated with KOH (0.4 g) in 95 % ethanol (52 ml) under stirring at 45° C for 40 minutes. The reaction mixture is then diluted with ice water and acidified to pH 4 with citric acid. The precipitate is filtered, washed with water until neutral and dried in vacuo at 80° C to yield 1,4-dihydro-5-(2-methoxyethoxymethoxy) methyl-1-phenyl-indeno[1,2-c]pyrazole-3-carboxylic acid (3.95 g), which is dissolved in anhydrous dioxane (50 ml) and reacted with oxalyl chloride (1.9 ml) in the presence of dimethylformamide (11 mg) at room temperature for 1 hour. The reaction mixture is evaporated to dryness in vacuo and the residue, crude 1,4-dihydro-5-(2-methoxyethoxymethoxy)methyl-1-phenyl-indeno[1,2-c]-pyrazole-3-carbonyl chloride, is dissolved in anhydrous dioxane (50 ml) and reacted for 1 hour under stirring at room temperature with the carbanion obtained by treatment of [illegible]-acetamide (1.76 g) with 50% sodium hydride (0.6 g) in anhydrous dioxane (140 ml). The reaction mixture is then diluted with ice water and acidified to pH 3 with 2N HCl.

The precipitate is filtered, washed with water and crystallized from CH_2Cl_2 isopropanol to yield 2-cyano-3-[1,4-dihydro-5-(2-methoxyethoxymethoxy)methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl]-3-oxo-N-phenyl-propanamide (1.5 g), which is suspended under stirring in methanol (800 ml) containing 37% HCl (8 ml) and heated at 45° C for 20 hours. After cooling the reaction mixture is concentrated in vacuo to a small volume and diluted with ice water. The precipitate is filtered and washed with water until neutral. Crystallization from CH_2Cl_2 methanol yields 1.05 g of 2-cyano-3-(1,4-dihydro-5-hydroxymethyl-1-phenyl-indeno[1,2-c]pyrazol-3-oxo-N-phenyl-propanamide.

By proceeding analogously the following compounds can be prepared:
2-cyano-3-(1,4-dihydro-7-hydroxymethyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-5-hydroxymethyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide; and
N-(3-chloro-phenyl)-2-cyano-3-(1,4-dihydro-5-hydroxymethyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide.

Example 21

3-(7-carboxy-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide(1.6 g) dissolved in anhydrous acetonitrile (100 ml) is reacted with N,N-dimethylaminoethanol (0.73 g), in the presence of dicyclohexylcarbodiimide (1.12 g) and 4-dimethylaminopyridine (0.265 g), under stirring at room temperature for 24 hours.
The precipitate is filtered off and the organic solution is concentrated in vacuo to a small volume. The residue is diluted with water, acidified to pH 2 with N HCl and then basified to pH 8 with N NaOH. The precipitate is filtered and purified over a SiO_2 column using chloroform (methanol) 30% NH_4OH 80/20 0.3 as eluent. The recovered product is dissolved in dimethylformamide (20 ml), acidified to pH 2 with 2N HCl, diluted with water (50 ml) and then basified to pH 8 with 2N NaOH. The precipitate is filtered and washed with water to yield 0.4 g of 2-cyano-3-(1,4-dihydro-7-N,N-dimethylaminoethoxycarbonyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.

By proceeding analogously the following compounds can be prepared:
2-cyano-3-(1,4-dihydro-5-N,N-dimethylaminoethoxycarbonyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide;
2-cyano-3-(1,4-dihydro-7-morpholinoethoxycarbonyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide; and 2-cyano-3-(7-N,N-dimethylaminopropoxycarbonyl-1,4-dihydro-1-phenyl-indeno[1,2-c]-pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.

Example 22

2-cyano-3-(1,4-dihydro-5-hydroxymethyl-1-phenyl-indeno [1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide (1,1 g) is reacted with succinic anhydride (0.8 g) in anhydrous pyridine (40 ml) under stirring at 45° C for 20 hours. After cooling the reaction mixture is diluted in ice water and the precipitate is filtered and washed with water. Crystallization from CH_2Cl_2 isopropanol yields 0.85 g of 3-[5-(3-carboxy-propanoyloxymethyl)-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl]-2-cyano-3-oxo-N-phenyl-propanamide

By proceeding analogously the following compound can be prepared:
3-[7-(3-carboxy-propanoyloxymethyl)-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl]-2-cyano-3-oxo-N-phenyl-propanamide.

Example 23

Tablets, each weighing 150 mg and containing 50 mg of active substance, can be manufactured as follows:

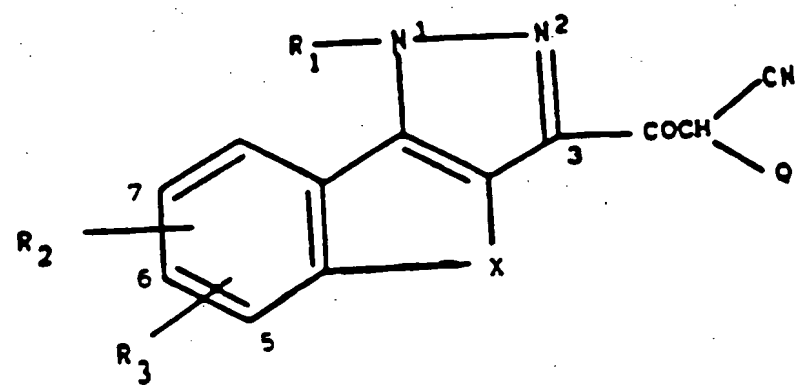
Composition (for 10 000 tablets)	
2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide	500 g
Lactose	710 g
Corn starch	238 g
Talc powder	36 g
Magnesium stearate	16 g

2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide, lactose and half of the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm openings. Corn starch (18 g) is suspended in warm water (180 ml). The resulting paste is used to granulate the powder. The granules are dried, comminuted on a sieve of sieve size 1.4 mm, then the remaining quantity of starch, talc and magnesium stearate is added, carefully mixed and processed into tablets using punches of 8 mm diameter.

By proceeding analogously, tablets can be prepared having the same composition, but containing, for example, as active substance one of the following compounds:
2-cyano-N-(4-fluoro-phenyl)-3-[1-(4-fluoro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-3-oxo-prupanamide;
2-cyano-N-(4-fluoro-phenyl)-3-(7-fluoro-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
and
2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-7-methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide.

Claims

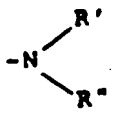
1. A compound of formula (I)



(I)

wherein
X represents:
a) a

group wherein R_4 is hydrogen, C_1-C_6 alkyl or a



group wherein each of R' and R'' independently is C_1-C_6 alkyl or R' and R'' taken together with the nitrogen atom to which they are linked, form a heterocyclic ring which is selected from N-pyrrolidinyl, N-

piperazinyl, hexahydroazepin-1-yl, thiomorpholino, morpholino and piperidino and which is unsubstituted or substituted by C_1-C_4 alkyl; or

b) an oxygen atom or a $-S(O)_n-$ group, wherein n is zero, 1 or 2; R_1 represents C_1-C_4 alkyl, pyridyl or phenyl, the phenyl being unsubstituted or substituted by one or two substituents chosen independently from halogen, trifluoromethyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, amino, formylamino and C_2-C_4 alkanoylamino;

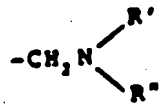
each of R_2 and R_3 is independently

a') hydrogen, halogen, C_1-C_4 alkyl or trifluoromethyl;

b') hydroxy, C_1-C_4 alkoxy or C_3 or C_4 alkenyloxy;

c') nitro, amino, formylamino or C_2-C_8 alkanoylamino;

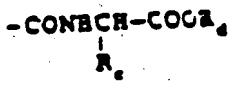
d') di(C_1-C_4 alkyl)amino or a



wherein R' and R'' are as defined above;

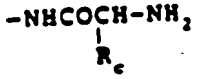
e') CH_2OH, CHO, COOH or C_2-C_7 alkoxycarbonyl;

f') a



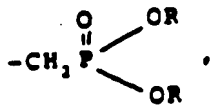
group wherein R_d is hydrogen or C_1-C_4 alkyl and R_c is hydrogen, phenyl or the side-chain of an α-aminoacid;

g') a



group, wherein R_c is as defined above;

h') a

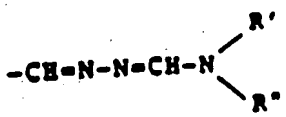


a $-CH_2OCO(CH_2)_nCOOR$ or a $-NHCO(CH_2)_nCOOR$ group, wherein n is as defined above and R is hydrogen or C_1-C_6 alkyl;

k') a $-CH=N-OR'_1$ group wherein R'_1 is hydrogen or a $-CH_2COOH$ group;

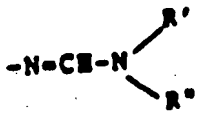
l') a $-CH=N-NH-R'_2$ group wherein R'_2 is hydrogen, $-CH_2CH_2OH$, C_2 or C_3 alkoxycarbonyl or a $-(CH_2)_p-R'_3$ group wherein p is 1 or 2 and R'_3 is COOH or C_2-C_7 alkoxycarbonyl;

l') a

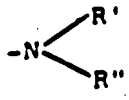


group wherein R' and R'' are as defined above; or

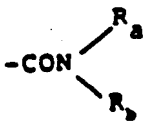
m') a



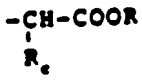
group wherein R' and R" are as defined above, or
n) a C_2-C_7 alkoxycarbonyl group substituted by a



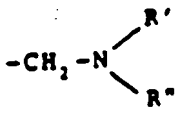
group, wherein R' and R" are as defined above; and
Q represents hydrogen, carboxy, C_2-C_7 alkoxycarbonyl or a



group wherein R_a represents hydrogen or C··C_{20} alkyl and R_b represents C··C_{20} alkyl, a



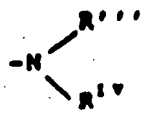
group wherein R and R_c are as defined above or a -$(A)_m$-R_5 group wherein m is zero or 1, A is a C··C_6 alkylene chain and R_5 is
a") C_5-C_8 cycloalkyl;
b") pyridyl, unsubstituted or substituted by one or two substituents chosen independently from halogen, C··C_6 alkyl and C··C_6 alkoxy;
c") phenyl, unsubstituted or substituted by one or two substituents independently chosen from halogen, CF_3, C··C_6 alkyl, C··C_6 alkoxy, amino, nitro, formylamino, C_2-C_8 alkanoylamino, di(C··C_6 alkyl)amino, hydroxy, CH_2OH, COOH, C_2-C_7 alkoxycarbonyl, formyloxy, C_2-C_8 alkanoyloxy and a



group wherein R' and R" are as defined above,
d") 2-thienyl, 2-furyl or 1-(C··C_6 alkyl)-pyrrol-2-yl; or
e") a heterocyclic ring which is selected from 2-pyrimidyl, 2-thiazolyl and 3-isoxazolyl and which is unsubstituted or substituted by C··C_6 alkyl;
and the pharmaceutically acceptable salts thereof.

2. A compound of formula (I) according to claim 1, wherein X is
a") a

group wherein R'_4 is hydrogen, C··C_6 alkyl or a

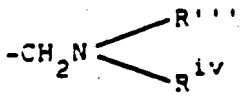


group wherein each or $R^{''}$ and R^{IV} independently is C_1 or C_2 alkyl or $R^{''}$ and R^{IV}, taken together with the nitrogen atom to which they are linked, form a heterocyclic ring which is selected from N-pyrrolidinyl, N-piperazinyl, morpholino and piperidino and which is unsubstituted or substituted by methyl; or b") oxygen or a $-S(O)_n-$ group, wherein n is as defined above;

R_1 represents unsubstituted pyridyl; or phenyl unsubstituted or substituted by one or two substitutents chosen independently from halogen, trifluoromethyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, amino and C_2-C_8 alkanoylamino;

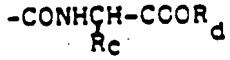
R_2 and R_3 each independently is

a°) hydrogen, halogen, hydroxy COOH, CHO, CH_2OH, CF_3, C_2-C_7 alkoxycarbonyl, nitro, amino, C_1-C_4 alkyl, C_1-C_4 alkoxy or a



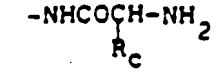
group wherein $R^{''}$ and R^{IV} are as defined above;

b°) a



group wherein R_d is hydrogen or C_1-C_6 alkyl and R_c is hydrogen, phenyl or the side-chain an α-amino-acid as defined above;

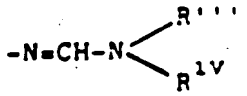
c°) a



group, wherein R_c is as defined above; d°) a $-CH_2OCO(CH_2)_nCOOR_d$ or a $-NHCO(CH_2)_nCOOR_d$ group, wherein n and R_d are as defined above.

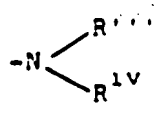
e°) a $-CH=N-OR_1$ group, wherein R_1 is hydrogen or a $-CH_2COOH$ group;

f°) a



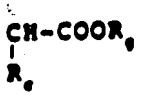
group wherein $R^{''}$ and R^{IV} are as defined above.

g°) a C_2-C_6 alkoxycarbonyl group substituted by a



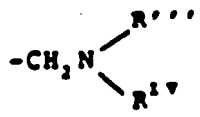
group, wherein $R^{''}$ and R^{IV} are as defined above.

Q represents hydrogen, C_1-C_4 alkoxycarbonyl or a $-CONR_aR_b$ group wherein R_a is hydrogen or C_1-C_6 alkyl and R_b is C_1-C_6 alkyl, a



group wherein R_2 is hydrogen or C_1-C_4 alkyl and R_c is as defined above, or a-$(A)_m$-R_5 group wherein m is zero or 1, A is a C_1-C_3 alkylene chain and R_5 is:

a^{IV}) unsubstituted pyridyl, or phenyl unsubstituted or substituted by one or two substitutents chosen independently from halogen, CF_3, C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro, CH_2OH, COOH, di-(C_1-C_4 alkyl)amino, hydroxy, formyloxy, C_2-C_6 alkanoyloxy and a



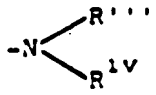
group wherein R^{III} and R^{IV} are as defined above;

b^{IV}) 2-thienyl or 2-furyl; or

c^{IV}) a heterocyclic ring which is selected from 2-thiazolyl or 3-isoxazolyl and which is unsubstituted or substituted by methyl; and the pharmaceutically acceptable salts thereof.

3. A compound of formula (I), according to claim 1, wherein X is oxygen, sulphur or a

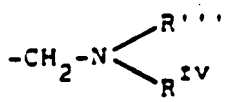
group wherein R''_4 is hydrogen, methyl or a



group wherein R^{III} and R^{IV} are as defined above;

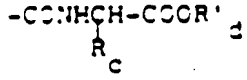
R_1 represents phenyl unsubstituted or substituted by a substituent selected from nitro, halogen, CF_3, C_1-C_4 alkyl and C_1-C_4 alkoxy; each of R_2 and R_3 independently is

a^{**}) hydrogen, halogen, COOH, CHO, CH_2OH, C_2-C_5 alkoxycarbonyl, CF_3, nitro, amino, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, or a



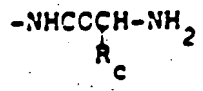
group wherein R^{III} and R^{IV} are as defined above;

b^{**}) a



group, wherein R'_3 is hydrogen or C_1-C_4 alkyl and R_c is as defined above

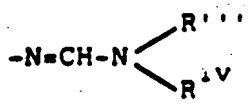
c'') a



group wherein R_c is as defined above.

d'') a $-CH_2OCO(CH_2)_nCOOR'_d$ or a $-NHCO(CH_2)_nCOOR'_d$ group, wherein n and R'_d are as defined above.

e'') a



group, wherein R''' and R^{IV} are as defined above;

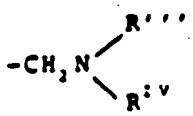
f'') a C_2-C_6 alkoxycarbonyl group substituted by a

group, wherein R''' and R^{IV} are as defined above;

Q represents hydrogen, C_2 or C_3 alkoxycarbonyl or a $-CONR'_aR'_b$ group wherein R'_a is hydrogen or C₁-C_6 alkyl and R'_b is C₁-C_6 alkyl, a

group wherein R_g and R_c are as defined above or a $-(CH_2)_p-R''_5$ group in which p is zero, 1 or 2 and R''_5 is:

a^V) unsubstituted pyridyl; or phenyl unsubstituted or substituted by one or two substituents chosen independently from nitro, halogen, CF_3, C₁-C_6 alkyl, C₁-C_6 alkoxy, CH_2OH, COOH, di(C₁- or C_2 alkyl) amino, hydroxy, formyloxy, C_2-C_6 alkanoyloxy and a



group wherein R''' and R^{IV} are as defined above;

b^V) 2-thienyl or 2-furyl; or

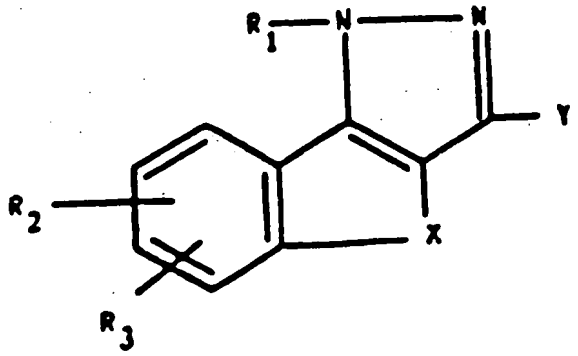
c^V) a heterocyclic ring which is selected from 2-thiazolyl or 3-isoxazolyl and which is unsubstituted or substituted by methyl; and the pharmaceutically acceptable salts thereof

4. A compound according to claim 1 selected from

2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide;
2-cyano-3-(7-fluoro-1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-[1-(4-fluoro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl]-3-oxo-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-7-methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
N-(3-chloro-phenyl)-2-cyano-3-[1-(4-fluoro-phenyl)-1,4-dihydro-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
2-cyano-N-(4-fluoro-phenyl)-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
N-(3-chloro-phenyl)-2-cyano-3-(1,4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-propanamide;
2-cyano-3-(1,4-dihydro-4-methyl-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.

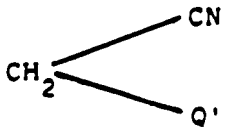
2-cyano-3-(1,4-dihydro-7-methyl-1-phenyl-indeno[1.2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide.
N-[2-cyano-3-(1 4-dihydro-1-phenyl-indeno[1.2-c]pyrazol-3-yl)-3-oxo-propanoyl]-glycine.methyl ester:
N-[2-cyano-3-(1.4-dihydro-1-phenyl-indeno[1.2-c]pyrazol-3-yl)-3-oxo-propanoyl]-glycine:
2-cyano-3-oxo-3-(1-phenyl-1H-benzothieno[3.2-c]pyrazol-3-yl)-N-phenyl-propanamide:
2-cyano-N-(4-fluoro-phenyl)-3-oxo-3-(1-phenyl-1H-benzothieno[3.2-c]pyrazol-3-yl]-propanamide:
2-cyano-N-(4-fluoro-phenyl)-3-[1-(4-fluoro-phenyl)-1H-benzothieno[3.2-c]pyrazol-3-yl]-3-oxo-propanamide:
2-cyano-N-(4-fluoro-phenyl)-3-(7-fluoro-1.4-dihydro-1-phenyl-indeno[1.2-c]pyrazol-3-yl)-3-oxo-propanamide:
3-(7-amino-1.4-dihydro-1-phenyl-indeno[1.2-c]pyrazol-3-yl)-2-cyano-3-oxo-N-phenyl-propanamide:
2-cyano-3-(5-ethoxycarbonyl-1.4-dihydro-1-phenyl-indeno[1.2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide:
N-[1,4-dihydro-1-phenyl-3-(2-phenylcarbamoyl-cyanoacetyl)-indeno[1.2-c]pyrazol-7-yl]carbonyl-glycine methyl ester:
2-cyano-3-(7-ethoxalylamino-1.4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide:
2-cyano-3-(1.4-dihydro-7-N.N-dimethylaminoethoxycarbonyl-1-phenyl-indeno[1.2-c]pyrazol-3-yl)-3-oxo-N-phenyl-propanamide:
3-(7-tert.butyl-1.4-dihydro-1-phenyl-indeno[1,2-c]pyrazol-3-yl)-2-cyano-N-(4-fluoro-phenyl)-3-oxo-propanamide:
2-cyano-N-(4-fluoro-phenyl)-3-(1.4-dihydro-1-phenyl-7-trifluoromethyl-indeno[1.2-c]pyrazol-3-yl)-3-oxo-propanamide.
and the pharmaceutically acceptable salts thereof.

5. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1, the process comprising:
a) reacting a compound of formula (II)



(II)

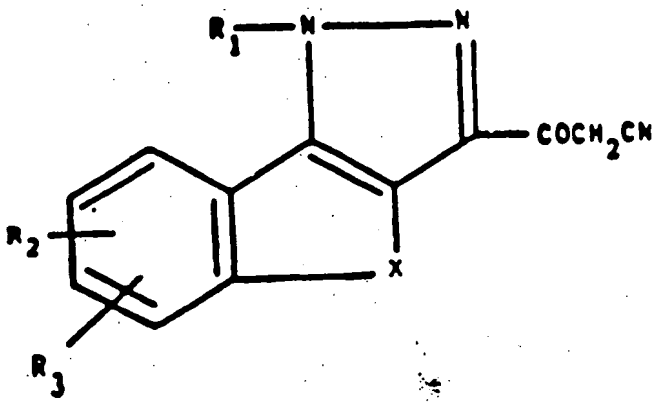
wherein
X, R_1, R_2 and R_3 are as defined in claim 1 and Y is carboxy or a reactive derivative of a carboxy group,
with a compound of formula (III)



(III)

wherein
Q' is as Q defined in claim 1 except carboxy, so obtaining a compound of formula (I), wherein Q is as defined in claim 1, except carboxy; or

b) reacting a compound of formula (IV)



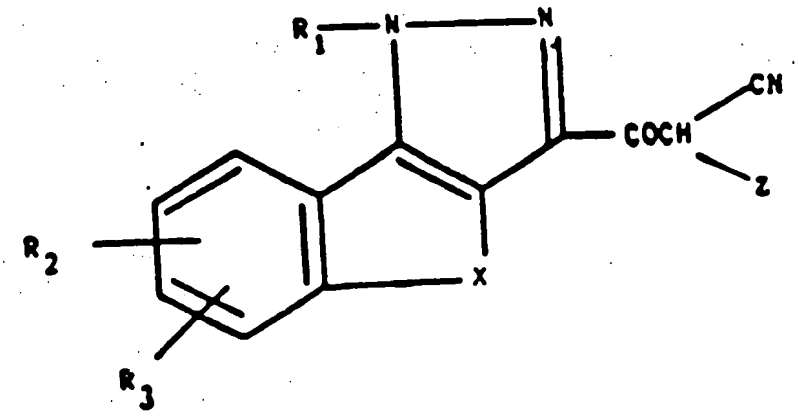
(IV)

wherein
X, R_1, R_2 and R_3 are as defined in claim 1, with a compound formula (V)

R_b-N=C=O (V)

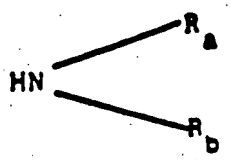
wherein
R_b is as defined in claim 1, so obtaining a compound of formula (I) wherein Q is a -CONHR_b group, wherein R_b is as defined in claim 1; or

c) reacting a compound of formula (VI)



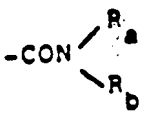
(VI)

wherein
X, R_1, R_2 and R_3 are as defined in claim 1 and Z is a reactive derivative of a carboxy group, with a compound of formula(VII)

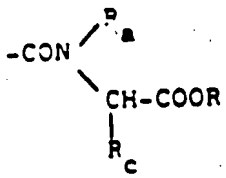


(VII)

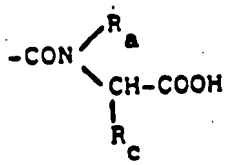
wherein
R_a and R_b are as defined in claim 1, so obtaining a compound of formula (I) wherein Q is a



group, wherein R_a and R_b are as defined in claim 1, or
d) hydrolysing a compound of formula (I), wherein Q is a C_2-C_7 alkoxycarbonyl or



group in which R_a and R_c are as defined in claim 1 and R is C_1-C_6 alkyl, so as to obtain the corresponding compound of formula (I), wherein Q is a free carboxy group or a



group, in which R_a and R_c are as defined in claim 1; and, if desired, converting a compound of formula (I) into another compound of formula (I) and/or, if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound, and/or, if desired, separating a mixture of isomers of a compound of formula (I), into the single isomers.

6. A pharmaceutical composition containing a pharmaceutically acceptable carrier and/or diluent and, as an active principle, a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof.

7. A compound of formula (I) or a pharmaceutically acceptable salt thereof, according to claim 1, for use as an immunostimulant agent.

8. A compound of formula (I) or salt thereof according to claim 7, for use in the treatment of an acute or chronic infection of bacterial or viral origin.

9. A compound of formula (I) or salt thereof according to claim 7, for use in the treatment of a neoplastic disease.

10. Use of a compound of formula (I) or salt thereof as defined in claim 1 in the preparation of a medicament for use as an immunostimulant agent.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 11 0986

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP-A-0 015 156 (SQUIBB & SONS, INC.)		C 07 D 231/54 A 61 K 31/425 C 07 D 401/04 C 07 D 491/048 C 07 D 495/04
A	US-A-3 004 983 (B. LOEV)		
A	US-A-2 989 538 (M.C. FLORES et al.)		
A	US-A-4 420 476 (A. PHILIPP et al.)		
A	US-A-4 431 657 (A. PHILLIP et al.)		
A	US-A-4 140 785 (H.E. HOFFMAN et al.)		
A	EP-A-0 005 357 (E.I. DU PONT DE NEMOURS AND CO.)		
P,A	EP-A-0 286 346 (E.I. DU PONT DE NEMOURS AND CO.)		

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 231/00
A 61 K 31/00
C 07 D 401/00
C 07 D 491/00
C 07 D 495/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	12-09-1989	DE BUYSER I.A.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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